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Clinical report

Docetaxel in 253 previously treated patients with progressive locally advanced or metastatic breast cancer: results of a compassionate use program in The Netherlands

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The aims of this study were to evaluate the efficacy and safety of docetaxel (Taxotere®) in patients with progressive locally advanced or metastatic breast cancer, previously treated with at least one chemotherapy regimen, and the effect of the number of previous chemotherapy lines on response rate, progression-free survival and overall survival. Two-hundred and fifty-three patients from 10 hospitals in The Netherlands received docetaxel as part of a compassionate use program. The majority had received prior anthracycline-containing chemotherapy (84.2%). The recommended starting dose was 100 mg/m^2 i.v. every 3 weeks. All patients received corticosteroid premedication. Two-hundred and thirty patients were evaluable for response. The overall response rates (ORR) to docetaxel when used as second-, third- or fourth-line treatment were, respectively, 40.2, 26.0 and 34.6% (*p* value 0.30). The median progression-free survival for this population was 4.9 months and the median overall survival of the whole group was 8.5 months, and both were not related to the number of previous chemotherapy regimens (*p* value, respectively, 0.71 and 0.16). The toxicity of docetaxel was manageable and neutropenia was the most frequently noted toxicity. This study confirms that docetaxel is an active cytotoxic agent in pretreated patients with progressive locally advanced or metastatic breast cancer and is still active when used as third- or fourth-line treatment.

Key words: Breast cancer, chemotherapy, docetaxel, overall survival, progression-free survival, toxicity.

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Introduction

Breast cancer is the most common malignancy in women in western countries. In The Netherlands each year approximately 10 000 patients are diagnosed with breast cancer. At initial presentation, the disease is often localized or extends to regional lymph nodes only. Under these circumstances treatment is directed to achieve cure. Once metastatic disease has been diagnosed, the prognosis is poor. Palliative cytotoxic therapy, e.g. containing an anthracycline, can be useful in these patients not previously treated with these agents. Recently the taxanes, paclitaxel and docetaxel, have increased the number of active drugs for women with breast cancer. Both agents are partly non-cross resistant with the anthracyclines. Docetaxel is a semisynthetic taxoid drug, made from a precursor extracted from the needles of the European yew, *Taxus baccata*. The mechanism of action is similar to that of paclitaxel. Docetaxel enhances microtubule assembly and inhibits tubulin depolymerization, thereby disrupting cell division. Docetaxel has a greater affinity than paclitaxel for the tubulin-binding site and it promotes structurally different microtubules. In preclinical studies docetaxel has demonstrated greater antitumor activity than paclitaxel at equitoxic doses. There is only partial cross-resistance between paclitaxel and docetaxel.[1–4] Several phase II studies have demonstrated significant activity when used as first- or second-line treatment of patients with metastatic breast cancer with response rates varying between 44 and 68%.[5–12] Studies have shown that response

rates to docetaxel are lower in heavily pretreated patients (more than two regimens)[13] and in patients who were defined as anthracycline resistant.[7,14]

In addition to its use as a single agent, docetaxel is currently being studied in combination chemotherapy in phase I/II trials with agents such as epirubicin, doxorubicin, mitoxantrone, cyclophosphamide, vinorelbine and gemcitabine.[15–19] Also studies are ongoing about its use in the (neo)-adjuvant setting and dose-dense (weekly) schedules.[20–22] Recently, a large randomized phase III study reported docetaxel to be superior to vinblastine plus mitomycin C in patients who had received previous anthracycline-containing chemotherapy.[23] The recommended dose is 100 mg/m^2 in a 1 h infusion every 3 weeks. The most common toxicities already described are alopecia, neutropenia, fatique, skin and nail toxicity, and cumulative dose-related fluid retention The latter can be diminished by the administration of corticosteroids.[24] For study in a less-defined patient cohort than in a phase II study, docetaxel was made available in The Netherlands on a named patient basis, as part of a compassionate use program between June 1994 and February 1996, the period immediately preceding commercial availability. We report here the efficacy and safety of docetaxel in patients with progressive locally advanced or metastatic breast cancer previously treated with at least one chemotherapy regimen, who participated in this program. We also investigated the effect of previously administered chemotherapy regimens on response rate, progression-free survival and overall survival following treatment with docetaxel.

Patients and methods

Eligibility criteria

Patients with histologically confirmed progressive locally advanced or metastatic breast cancer were eligible for this study. Patients were required to be at least 18 years of age and to provide informed consent according to the local Ethics Committee requirements. All patients must have received at least one prior chemotherapy regimen for the treatment of locally advanced or metastatic disease prior to treatment with docetaxel. Prior taxane therapy was allowed except for the first-line treatment of metastatic disease. At entry patients were not required to have measurable or evaluable disease. They had to have adequate hematological, renal and hepatic functions [ANC $\geqslant 2.0 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, total bilirubin $\leqslant 1.25 \times$ upper normal limit; AST (SGOT) and/or ALT (SGPT) $\leqslant 5 \times$ upper normal limit; alkaline phosphatase $\leqslant 6 \times$ upper normal limit (unless bone metastases were present in the absence of any liver disorder); creatinine $\leqslant 1.5 \times$ upper normal limit]. All patients had to have a Karnofsky performance status of 60% or WHO $\leqslant$ grade 2, estimated life expectancy of at least 12 weeks and practice appropriate contraception methods if indicated. Exclusion criteria were: clinically evident brain metastases; history of prior malignancy except completely excised *in situ* carcinoma of the cervix or non-melanoma skin cancer; other serious illness; concurrent symptomatic grade II or greater peripheral neuropathy according to the NCI common toxicity criteria; concurrent treatment with other experimental drugs.

Study drug, treatment plan and dose modifications

Docetaxel (Taxotere RP 56976) was supplied by Rhône-Poulenc Rorer (Antony, France) as a concentrated sterile solution containing per vial 80 mg drug in 2 ml of polysorbate 80 (Tween 80®). The drug was prediluted with ethanol/95% water (13/87, w/w) to obtain an intermediate solution of 10 ng/ml docetaxel. Thereafter, the appropriate amount of the drug was diluted further in a dextrose 5% solution to obtain a maximal concentration of 1 mg/ml. Treatment consisted of docetaxel 100 mg/m^2 as a 1 h infusion i.v. every 3 weeks. Patients with impaired liver function, defined as with AST (SGOT) and/or ALT (SGPT) $> 1.5 \times$ upper normal limit associated with alkaline phosphatase $> 2.5 \times$ upper normal limit, were treated at a reduced dose of 75 mg/m^2. A routine prophylactic corticosteroid medication was required before and during the first few days of each treatment cycle (dexamethasone 8 mg *per os* b.i.d. to be given days -1, 1, 2, 3 and 4). Dose reductions of 25% were mandated for patients who experienced grade 3 or grade 4 neutropenia associated with $\geqslant$ grade 2 fever, grade 3 nausea and vomiting despite anti-emetic treatment, grade 2 peripheral neuropathy, grade 3 bilirubin levels and grade 2 or 3 of AST/ALT/alkaline phosphatase levels and other non-hematological toxicity $\geqslant$ grade 3, except for alopecia. Patients were withdrawn from study in case of grade 4 hypersensitivity reactions and neuropathy $\geqslant$ grade 3 and severely impaired liver function in absence of progressive disease (AST/ALT/alkaline phosphatase $>$ grade 3, bilirubin grade 4). For patients who required dose reduction, the dosage was not re-escalated in subsequent cycles. Only two dose reductions were allowed, first to 75 mg/m^2, then to 55 mg/m^2, and patients who required further dose reductions were withdrawn from the study.

Assessment of response, toxicity and follow-up

Hematological parameters were measured weekly, other parameters including performance status, biochemistry, toxicity evaluation and clinical tumor measurement were to be checked at each 3-weekly visit. Response was evaluated according to the WHO criteria. WHO criteria were defined as following: complete response (CR) is the disappearance of all known disease determined by two observations not less than 4 weeks apart and partial response (PR) is defined as a decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions, determined by two observations not less than 4 weeks apart. No change (NC), lasting for at least 6 weeks from start of the study of drug administration, is defined as $<50\%$ decrease and $<25\%$ increase in the sum of the products of the largest perpendicular diameters of all measurable lesions, and progressive disease (PD) as $>25\%$ increase in the size of at least one bidimensionally or unidimensionally measurable lesion or appearance of a new lesion. The occurrence of pleural effusion or ascites is also considered as PD if this is substantiated by positive cytology. The duration of CR, PR or NC is recorded from the start of treatment until documentation of progression. Response duration was censored for start of further anti-tumor treatment. Progression-free survival was calculated for all patients from the time of study entry until tumor progression or death. Survival time was calculated for all patients from the day of start of docetaxel treatment (study entry) until death or 1 April 1998 (cut-off date of analysis).

Generally, six cycles was considered the maximum duration of treatment, especially for patients with stable disease. Patients with disease progression and/or unacceptable toxicity could finish treatment earlier.

Patients showing a response were allowed to receive an additional three or more cycles when this was considered to be in the best interest of the patient. Toxicity was graded according to the NCI Common Toxicity Criteria (CTC) scale.[25] All patients who received at least one cycle of therapy were considered evaluable for toxicity.

Statistics

Analyses of response rate (RR), progression-free survival and overall survival were performed on all patients. Confidence intervals for RRs were calculated using methods for exact binomial confidence intervals. Progression-free survival curves and overall survival curves were based on Kaplan–Meier estimates,[26] and comparisons were performed using the log-rank test. Comparison of response rates between independent groups of patients were calculated with Kruskal–Wallis test.

Results

Patient characteristics

A total of 253 patients (Table 1) from 10 hospitals in The Netherlands were entered onto the study with a median age of 51 years (range 29–84). All patients had received at least one prior chemotherapy regimen for

Table 1. Patient characteristics (n=253)

Characteristic		No. of patients	%
Age (years)			
median	51		
range	29–84		
WHO performance score			
median	1		
range	0–2		
Primary tumor, at diagnosis (stage)			
unknown		29	11.4
I		43	17
II		103	40.7
III		53	21.0
IV		25	9.9
Tumor involvement at start of treatment			
primary breast		17	6.7
liver		160	63.2
bone		108	42.7
lung		101	39.9
skin		106	41.9
lymph nodes		76	30.0
other		52	20.6
Prior therapy			
hormonal		217	85.8
radiotherapy		182	72
chemotherapy		253	100
Prior chemotherapy			
(neo)adjuvant		86	34
metastatic		232	91.7
Number of previous chemotherapy regimens			
1		95	37.5
2		103	40.7
3		55	21.8
Anthracycline-containing chemotherapy			
total		213	84.2
first-line		127	59.6
second-line		73	34.3
third-line		13	6.1
Prior taxanes (paclitaxel)		8	3.2
Median time diagnosis–start docetaxel			
months	51		
Median time last chemotherapy–start docetaxel			
months	3		

progressive locally advanced or metastatic disease. At start of treatment with docetaxel, 232 patients (91.7%) had metastatic disease, most of them with visceral involvement. Two-hundred and thirteen patients (84.2%) were previously treated with anthracyclines—the majority for the first-line treatment of metastatic disease (Table 1). One-hundred and fifty-eight patients (62.5%) were previously treated with two or more chemotherapy regimens, before starting treatment with docetaxel. Eight patients received prior paclitaxel, but not for the first-line treatment of metastatic disease. Most of the patients received prior hormonal treatment (85.8%) as well as radiotherapy (72%).

Toxicity

All 253 patients were evaluable for toxicity and the maximum severity grade of the non-hematological toxicity during treatment is shown in Table 2. Grade 1 or 2 side effects that are known for treatment with docetaxel, such as alopecia, skin and nail changes, mild fluid retention or nausea were also seen in this study. Neurotoxicity was observed in 74.2% of all patients, but this was not severe and mostly transient. Eight patients (3.2%) experienced a grade 3 neurotoxicity and were taken off study. Mild stomatitis/mucositis was frequently seen.

Only one serious hypersensitivity reaction (HSR) was observed. This low incidence was probably due to the prophylactic administration of corticosteroids. The most serious side effect was neutropenia. Neutropenia grade 3 and 4 was observed in 94.3% of all cycles. However, only 67 courses (5.3%) were complicated by neutropenic fever, necessitating hospitalization and dose reduction (Table 3).

Dose delivery and reduction

Two-hundred and forty-three patients (96%) started the first course at a dose level of 100 mg/m^2. Nine patients started at a dose level of 75 mg/m^2 , because of impaired liver function and one patient received the first dose of 55 mg/m^2 for an unknown reason. A total of 1271 courses was administered to all the patients. Two-hundred and sixteen courses (17%) were dose-reduced, mainly due to (non)-hematological toxicity. Median delivered number of courses in the evaluable patients was 5 (range 1–14) with a dose intensity of $\geqslant$75 mg/m^2/3 weeks in 209 (90.9%) of the patients and a dose intensity of $<$75 mg/m^2/3 weeks in 21 patients (9.1%).

Anti-tumor response

Two-hundred and thirty patients were evaluable for response. As shown in Table 4 the overall response rates (ORR) to docetaxel when used as second-, third- or fourth-line treatment were, respectively, 40.2, 26.0

Table 3. Side effects of docetaxel therapy hematological side effects (all cycles *n*=1271)

Cycles	CTC grade			
	1 (%)	2 (%)	3 (%)	4 (%)
WBC	1.7	7.6	53.4	37.3
ANC	0.9	4.8	30.8	63.5
Neutropenic fever			5.3	

WBC, white blood cell count; ANC, absolute neutrophil count.

Table 2. Side effects of docetaxel therapy in patients non-hematological toxicity (*n*=253 patients)

Patients	Total (*n*/%)	Maximum severity grade (CTC grade)			
		1 (*n*/%)	2 (*n*/%)	3 (*n*/%)	4 (*n*/%)
HSR	26/10.3	20/7.9	5/2.0		1/0.4
Nausea	177/70.0	140/55.3	25/9.9	12/4.8	
Vomiting	102/40.3	58/22.9	31/12.3	9/3.5	4/1.6
Stomatitis/mucositis	201/79.4	125/49.4	57/22.5	15/5.9	4/1.6
Fluid retention	19/7.5	10/3.9	9/3.6		
Neurosensory	178/70.3	140/55.3	32/12.6	6/2.4	
Neuromotor	10/3.9	6/2.3	2/0.8	2/0.9	
Infection	51/20.0	16/6.3	20/7.9	7/2.8	8/3.2
Fever	80/31.6	11/4.3	60/23.7	7/2.8	2/0.7
Fatigue	181/71.5	69/27.3	86/34.0	24/9.5	2/0.8
Skin	142/56.1	98/38.7	39/15.4	3/1.2	2/0.7
Nail	145/57.3	106/41.9	36/14.2	3/1.2	

Table 4. Response to docetaxel after previous chemotherapy lines (*n*=230 evaluable patients)

Docetaxel	Complete response (*n*/%)	Partial response (*n*/%)	Stable disease (*n*/%)	Progressive disease (*n*/%)	Overall response (*n*/**%**) (*95% CI*)
Second line (*n*=82)	4/4.8	29/35.4	35/42.7	14/17.1	33/**40.2** *29.6–52.6*
Third-line (*n*=96)	0	25/26	44/45.8	27/28.1	25/**26** *17.6–36.0*
Fourth-line (*n*=52)	2/3.8	16/30.8	23/44.2	11/21.2	18/**34.6** *22.0–49.0*

p=0.30.

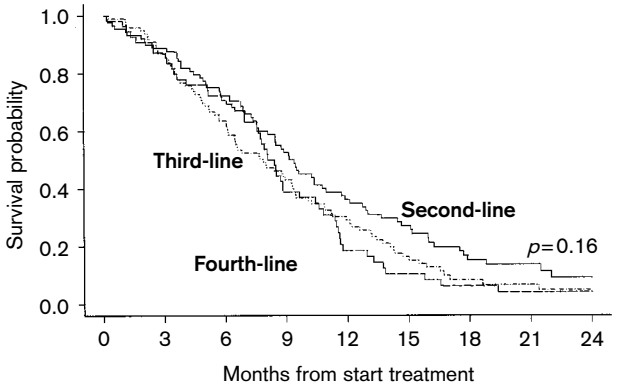

Figure 1. Overall survival of 230 evaluable patients treated with docetaxel in several lines.

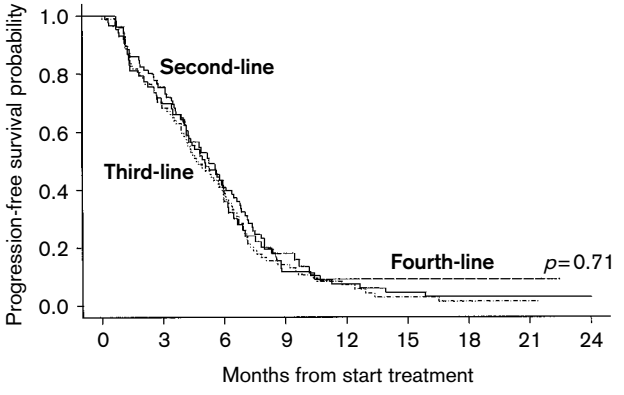

Figure 2. Progression-free survival of 230 evaluable patients treated with docetaxel in several lines.

and 34.6%, and were not related to the number of previous treatments (*p* value 0.30). The responses were observed at all sites of metastatic disease.

Eight patients received prior paclitaxel. Four of them developed progressive disease following treatment with docetaxel and four patients had stable disease.

Duration of response, progression-free survival and overall survival

Median follow-up time counting from the first day of treatment until 1 April 1998 was 22 months. Kaplan–Meier survival analysis of all evaluable patients yielded a median overall survival of 8.5 months (Figure 1) and a median progression-free survival of 4.9 months (Figure 2). The median overall response duration was 6 months. No association between the number of previous chemotherapy regimens and overall survival or progression-free survival could be detected (*p* value, respectively, 0.16 and 0.71) as shown in Figures 1 and 2.

Discussion

This large multicenter open study, which does not reflect a standard phase II or III clinical trial but a 'real life clinical setting' in 253 patients with advanced breast cancer, demonstrates that docetaxel used in the community setting is an active anti-cancer drug. Two-hundred and thirty patients who were evaluable for response showed ORR to docetaxel when used as second-, third- or fourth-line treatment of, respectively, 40.2, 26.0 and 34.6%. The response rates were not related to the number of previous chemotherapy lines (*p*=0.30). Most of the patients had received prior anthracycline-containing chemotherapy. Because of lack of data, it was not possible to define patients who were anthracycline-resistant or not.

Several phase II studies investigated the activity of docetaxel, and have shown response rates varying between 30 and 58% when docetaxel was administered as second-line treatment for advanced disease.[5,7,27] Our study confirms the published phase II studies and shows an ORR of 40.2% in the second-line treatment.

Our study also demonstrates that docetaxel is active even when administered as third- or fourth-line treatment. Recently, Archer *et al*. reported an ORR of 24% in heavily pretreated patients (more than two regimens), which was lower than the ORR in our study in patients with comparable prior treatment. He suggested that the bad clinical condition of the patients had caused the low ORR.[13] Possibly in our study there is a selection of patients in the third- or fourth-line treatment due to favorable conditions in this group. Our study yielded a median progression-free survival of 4.9 months and a median overall survival of 8.5 months. Neither the progression-free survival nor overall survival were related to the number of previous chemotherapy regimens. The first large randomized phase III trial (392 patients) published by Nabholtz *et al*. compared docetaxel with mitomycin C plus vinblastine (MV) in patients with metastatic breast cancer previously treated with anthracyclines. The results showed that the docetaxel arm is significantly superior to the MV arm in terms of ORR, time to progression (TTP) and overall survival. The docetaxel arm revealed an ORR of 30%, a median TTP of 19 weeks and a median overall survival of 11.4 months. The MV arm showed an ORR of 11.6%, a median TTP of 11 weeks and an overall survival of 8.7 months.[23] The results of these patients who were minimally pretreated (less than two regimens) are comparable with our results.

Toxicity in our study is comparable with other studies.[5–9] The serious and most frequently noted side effects were neutropenia and neutropenic fever. The incidence of fluid retention and hypersensitivity reactions was not frequently reported and was generally mild. This may have been due to the use of premedication with corticosteroids. Recently, a 3 day dexamethasone regimen was reported to be as effective as a 5 day regimen in ameliorating docetaxel-induced toxicity with less severe steroid-related side effects.[28]

Eight patients were previously treated with paclitaxel. None of them showed a PR or CR. Recently, Valero *et al*. showed that patients who were paclitaxel resistant can benefit from treatment with docetaxel, based on the finding that there is only partial cross-resistance with paclitaxel.[29] Our group of eight patients is too small for a confirmation of this observation.

Currently, combination chemotherapy studies are ongoing with docetaxel in metastatic disease as well as in the adjuvant setting, with the aim to improve prognosis and curability. Further development also aims at dose-dense therapy. Recently published results reveal that, for example, weekly scheduling can result in high anti-tumor activity.[22]

In conclusion, these data reflect the experience of clinical oncologists in general practice in The Netherlands and demonstrate that docetaxel is active in heavily pretreated patients with metastatic or progressive locally advanced breast cancer. Patients selected for formal clinical trials are not necessarily representative of the general population. Therefore, it is important to explore activity and efficacy in this expanded access program. The results of this study confirm the results of the first large randomized phase III trial with docetaxel.

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